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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/511,656

04/18/2005

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129402.00101

9867

21269 7590 10/14/2008
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EXAMINER

HILL, KEVIN KAI

ART UNIT

PAPER NUMBER

1633

MAIL DATE

DELIVERY MODE

10/14/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/511,656	Applicant(s) SCHULTE ET AL.	
	Examiner KEVIN K. HILL	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 July 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2-24, 26-28, 31, 46 and 48-55 is/are pending in the application.
- 4a) Of the above claim(s) 14-18, 23 and 55 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2-13, 19-22, 24, 26-28, 31, 46 and 48-54 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 24 July 2008 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>March 4, 2008</u> | 6) <input type="checkbox"/> Other: _____ |

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Detailed Action

Election/Restrictions

Applicant's response to the Requirement for Restriction, filed on October 29, 2007 is acknowledged. Applicant has elected without traverse the invention designated as Invention Group II, claims 2-31 and 46, directed to a method of using a composition comprising one or more double-stranded oligoribonucleotides (dsRNA) for the specific modulation of the expression of target genes in cells and/or tissues of the CNS and/or eye, wherein said composition is introduced into a cell, tissue or organism outside the blood-brain or blood-retina barrier.

Within Group II, Applicant has further elected the restricted neural tissue subgroup, cells and tissues of the eye.

Within Group II, Applicant has elected the following species:

- i) wherein the dsRNA molecule is dsRNA molecules between 21 and 23 nucleotides in length, as recited in claim 13,
- ii) wherein the promoter is a tissue specific promoter, as recited in claim 20,
- iii) wherein the dsRNA is complexed to a micellar structure, as recited in claim 22,
- iv) wherein the means by which the dsRNA is administered to the eyeball systemic administration, as recited in claim 26,
- v) wherein the eye disease is a degenerative retinal disease, as recited in claim 50, and
- vi) wherein the organism is human, as recited in claim 31.

Because Applicant did not distinctly and specifically point out the supposed errors in the Group or species restriction requirement, the election has been treated as an election without traverse and the restriction and election requirement is deemed proper and therefore made final (MPEP § 818).

Amendments

In the reply filed July 24, 2008, Applicant has cancelled Claims 1, 25, 29-30, 32-45 and 47, and amended Claims 2-7, 11-12, 15, 17-18, 20-24, 26, 31, 46, 50-52 and 55.

Claims 14-18, 23 and 55 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 2-13, 19-22, 24, 26-28, 31, 46 and 48-54 are under consideration.

Priority

This application is a 371 of PCT/EP03/04002, filed April 18, 2002. Applicant's claim for the benefit of a prior-filed application parent provisional application 60/431,173, filed December 5, 2002, under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

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Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). While a certified copy of the foreign patent application EPO 02008671.5, filed April 18, 2002, has been filed with the instant application, a certified English translation has not been provided.

The effective priority date of the instant application is granted as April 18, 2002.

Information Disclosure Statement

Applicant has filed an Information Disclosure Statement on March 4, 2008 that has been considered. Drumm (U.S. 2006/0003915) has been lined through because the Examiner has already entered this reference into the record. The signed and initialed PTO Form 1449 is mailed with this action.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the July 24, 2008 response will be addressed to the extent that they apply to current rejection(s).

Drawings

1. **The prior objection to the drawings is withdrawn** in light of the amendment (papers filed July 24, 2008) to Figure 1 labeling the panels and stating that the opacity is not an artifact.

Specification

2. **The prior objection to the disclosure is withdrawn** in light of the amendment (papers filed July 24, 2008) to correct the Brief Description of Figure 1.

Claim Objections

3. **The prior objection to Claims 20 and 26 is withdrawn** in light of Applicant's amendments to the claims.

4. **Claims 5 and 7 are objected to because of the following informalities:**

With respect to Claim 5, the phrase "the...dsRNSS" [emphasis added], should be "the...dsRNA".

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With respect to claim 7, the claim is grammatically awkward. The Examiner respectfully suggests the following recitation: "The method of claim 2, wherein the cells or tissues are cells or tissues of the eye."

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The prior rejection of Claims 2-13, 19-22, 24-28, 31, 46 and 48-54 under 35

U.S.C. 112, second paragraph, is withdrawn in light of Applicant's amendments to the claims to clarify the invention. Applicant's argument that those of ordinary skill in the art would understand what is meant by the limitation "inner segment of the eye ball" (claim 8) and "predominantly expressed" or "specific for" (claims 11-12) is considered persuasive.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. The prior rejection of Claims 2-13, 19-22, 24-28, 31, 46 and 48-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description

requirement is withdrawn in light of Applicant's amendment to the preamble, such that the instantly claimed method is "for delivery of oligoribonucleotides across the blood-brain or the blood-retina barrier".

7. Claims 5-6 and 50-53 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is maintained for reasons of record in the office action mailed January 24, 2008 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed July 24, 3008.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets

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the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is “undue” (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

The claims are broad because the method may be performed *in vitro* and *ex vivo* (both of which are “outside the blood-brain or blood-retina barriers”, as well as *in vivo*).

The breadth of the claims is exceptionally large for encompassing an enormous genus of undisclosed and structurally distinct dsRNA compositions that are capable of inhibiting the expression an enormous genus of structurally distinct target genes in the eye.

The breadth of the claims is exceptionally large for encompassing an enormous genus of composition formularies, e.g. naked dsRNA, liposomal carriers thereof, nucleic acid vectors expressing dsRNA, and liposomal carriers thereof, as well as gene therapy and cell-based therapy.

The breadth of the claims in combination with the fact that the specification discloses the intended use of the dsRNA in the method is for the therapeutic treatment of an enormous genus of etiologically and pathologically distinct diseases related to the eye (pg 2, ¶4; pg 4, lines 3-4) by “modulating a target gene” requires that these claims be evaluated to determine whether the specification provides teaches how to use these compositions and perform the claimed method for treating these conditions by modulating, i.e., increasing and decreasing, the expression of a target gene.

The claims are also broad for encompassing an enormous genus of animal organisms comprising a central nervous system and/or eyes, about 1,000,000 species of vertebrate and invertebrate animals (waynesword.palomar.edu/trfeb98.htm, last visited November 26, 2007), whereupon the enormous genus of eye diseases may be treated as per the claimed invention.

When the claims are analyzed in light of the specification, the inventive concept in the instant application is that dsRNA molecules of a length of 21 to 23 nucleotides are capable of, after systemic application, e.g. intravenous injection, or by retrobulbar injection, to cross the blood-retina barrier (pg 17, ¶3).

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The breadth of the claims requires evaluating the specification for enabling disclosure teaching one of skill how to use dsRNAs to inhibit the expression of a gene to treat the complete genus of disorders now embraced by the claims. That is, it is imperative that the specification or the prior art have taught one of skill at the time of filing how to correct the genus of eye disorders by inhibiting the expression of specific genes, gene families, or classes, which may be

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overexpressed or expressed as mutant isoforms sensitive to the effects of interference by dsRNA. One of skill would have needed to know which genes to target in order to effectively treat the disorder without undue experimentation. However comprehensive disclosure enabling one of skill to practice the full scope of the instant methods without undue experimentation is lacking.

The specification discloses that systemic application of double-stranded RNAs, also known in the art as small interfering RNAs (siRNA) generally gives rise to side effects outside the target organs eye and brain-often without significant quantities of active substance being detectable in the target tissue. Even with sufficient target specificity, which would minimize the risk of unwanted side effects of systemic application, this method of application remains inefficient, since the target tissue and target cells are located beyond the blood-brain or blood-retina barrier and the active substance is not able to reach its site of activity because of the stringent activity of this barrier. This problem has been solved by the present invention (pg 5).

Applicant contemplates the nucleic acids may be introduced into the cells or tissues bound to other molecules and/or combined with one or more suitable carriers, e.g. liposomes, coat proteins, and fusogenic peptides (pg 13, ¶1). The compositions of the invention may be administered locally, e.g. iontophoretically or by retrobulbar injection, or systemically, e.g. intravenously, subcutaneously, intrasynovially, or orally (pg 18, ¶2) at concentrations ranging between about 0.001µg to about 10mg units/day and/or units/kg body weight (pg 6, ¶3; pg 18, lines 1-6), wherein the dsRNA molecules inhibit the corresponding target gene(s) by post-transcriptional silencing.

“The central idea of the present invention is surprising in so far as dsRNA molecules of a length of 21 to 23 nucleotides are able to cross the blood-retina barrier, and specifically inactivate target genes in the tissues of the back of the eye, after systemic application, for example by intravenous injection. This overcoming the blood-retina barrier is all the more remarkable, because no experiment could demonstrate overcoming this barrier by dsRNA so far.” (pg 12, lines 1-6). “The method described in this invention is distinguished from the prior art by the fact that it could be shown for the first time that dsRNA molecules, preferably of the length specified above, can be detected inside the eye after systemic or local application outside the eyeball.” (pg 13, ¶2).

The working examples disclose that systemic administration by tail vein injection or local administration by retrobulbar injection of 200µg/kg of naked dsRNA in buffer targeted against an enhanced GFP transgene appears to be capable of inducing post-transcriptional gene silencing of the eGFP in the retina and retinal pigment epithelial cells in a mouse model.

The Examiner notes that while Experimental Procedures 2 and 4-5 appear to be designed to determine the optimal time of efficacy of post-transcriptional gene silencing, neither the specification nor the table disclose the result obtained--the optimal time of efficacy of post-transcriptional gene silencing. Similarly, while Experimental Procedure 3 appears to be designed to determine the optimal dsRNA concentration for post-transcriptional gene silencing, the table indicates only the use of 200µg/kg. Thus, the concentration variable was not even manipulated and compared to other concentrations as indicated by the preamble. Furthermore, neither the specification nor the tables disclose the result obtained-- the optimal dsRNA concentration for post-transcriptional gene silencing (pgs 28-30).

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The specification is not enabling because while the instant application provides working examples teaching one of skill how to deliver dsRNA to into cells in the eye of subject to inhibit the expression of a target gene in the cell by post-transcriptional gene silencing, the instant application fails to provide any disclosure showing how the administration of dsRNA may **increase** the expression of a gene in a cell in the eye, which is embraced by the limitation "capable of modulating a target gene" in claim 2. Further, a review of the prior art fails to find any evidence that dsRNAs of 21 to 23 nucleotides may specifically increase the expression or activity of a gene to treat an eye disorder.

Given the absence of such disclosure, the skilled artisan would not know *a priori* whether introduction of dsRNAs *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the agent reaching the proper cell in a sufficient concentration and remaining for a sufficient time to increase the expression of a target gene. Neither the specification nor the prior art provide the guidance necessary to teach one of skill how to increase the expression of a gene using dsRNA, and there is no evidence in the prior art or specification to even suggest that dsRNA is capable of such activities. Rather, a careful reading of the specification shows that Applicant's invention is directed to the inhibition of gene expression not enhancing gene expression. The latter is conventionally accomplished by expressing the full length gene not by administering short interfering RNA.

The specification is not enabling because neither it nor the prior art enable one of skill to practice the full scope of the methods now claimed without undue experimentation. The specification does not teach the enormous genus of genes specifically overexpressed or aberrantly expressed, i.e., as mutant isoforms in the complete genus of eye disorders of the enormous genus of animals encompassed by the claims, and how such expression is specifically related to the eye disorders embraced by and specifically recited in the instant claims. Such information is essential to the practice of the instant methods. While the specification provides enabling disclosure for delivering dsRNA into a mammalian (mouse) eye by administration outside the blood-retina barrier, the specification is not considered to be enabling for treating all possible eye disorders in the enormous genus of animals possessing eyes. Given the complexity of the biochemistry of such disorders, the distinctly different anatomical properties that comprise blood-retina barriers, and the many genes expressed in the eye which may or may not be directly related to the disorders, one of skill would require specific guidance as to how to design the dsRNAs effective for inhibiting the expression of a gene involved in any disorder in order to treat the disorder. Such comprehensive disclosure is lacking.

The specification is not enabling because it does not disclose those formulations and nucleic acid molecule concentrations necessary to overcome the art-recognized unwanted side effects outside the target organs eye and brain—often without significant quantities of active substance being detectable in the target tissue. The disclosed target gene, eGFP, is an exogenous gene, and thus does not reflect the existence of unwanted side effects caused by the expression of a developmentally important gene.

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

dsRNA

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The instant claims encompass the pharmaceutical use of the oligonucleotide compositions and formulations of the instant invention for treatment purposes. However, the specification as filed does not enable one skilled in the art to use the claimed pharmaceutical compositions or formulations for treatment purposes *in vivo*. In regards to the amount of direction or guidance presented, the specification as filed does not provide sufficient guidance or instruction that would teach one of skill in the art how to successfully practice a therapeutic method to treat a retinal degeneration disease or eye condition associated with the expression of a particular mRNA target, comprising the administering to a patient the double-stranded RNA compositions and formulations according to the present invention.

Regarding the level of predictability or unpredictability associated with the antisense therapeutic art, Crooke (Progress in Antisense Technology, in Methods of Enzymology 313:3-45, 1999, Academic Press), states "extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies [references omitted]." Furthermore, Crooke describes a variety of factors that influences the activity of antisense-based compounds. Crooke teaches that variations in cellular uptake and distribution of antisense oligonucleotides are influenced by a variety of factors: length of oligonucleotide, modifications, and sequence of oligonucleotide and cell type. The influence of non-antisense effects, for example phosphorothioate oligonucleotides tend to bind non-specifically to many proteins, wherein such protein binding influences cellular uptake, distribution, metabolism and excretion of said oligonucleotide. Additionally, non-specific protein binding may produce effects that can be mistakenly interpreted as antisense activity, and may also inhibit antisense activity of some oligonucleotides. In addition to proteins, oligonucleotides may non-specifically interact with other biological molecules, such as lipids, or carbohydrates, wherein the chemical class of oligonucleotide will influence such interactions studied (Crooke, 1999; p. 3). Crooke clearly teaches that there is a significant level of factors which influence the behavior of antisense based compounds thereby rendering the activity of antisense compounds unpredictable.

Caplen (Caplen, N.J., August, Gene Therapy 11(16): 1241-1248, 2004) reviews the progress and prospects of RNA interference methods triggered by double-stranded RNA. While RNAi appears to be easy to induce, critical analysis of RNAi derived phenotypic data should not be overlooked. The validation of the RNAi effect in mammalian cells is important and that non-specific effects of RNAi need to be carefully assessed in mammalian cells (pg 1245). For example, "ensuring the specificity and quantifying the efficacy of the particular siRNA or shRNA against a clinically relevant target transcript is essential in justifying its further development." And, Caplen states "it should be possible to rescue the functional phenotype induced by RNAi by expression of a transcript resistant to the siRNA under study."

Caplen addresses the degree of unpredictability in the art when choosing a biologically effective antisense sequence, stating that "it is unclear at this time (2004) what the minimum level of homology required between the siRNA and the target to decrease gene expression is, but it has been reported that matches of as few as 11 consecutive nucleotides can affect the RNA levels of a non-targeted transcript" (pg 1245, col. 2). This is especially relevant in mammalian cells because mammalian cells have nonspecific dsRNA-triggered responses primarily mediated

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through interferon-associated pathways that are absent in invertebrates and plants. Caplen expresses the importance in recognizing that there is variation in the degree of inhibition mediated by different small interfering RNA sequences which may result in the production of different phenotypes.

Delivery

In regards to the delivery of oligonucleotide pharmaceutical compositions *in vivo*, the state of the art indicates that delivery of these oligonucleotide compositions for therapeutic purposes "remains an important and inordinately difficult challenge (Chirila et al, January, Biomaterials 23:321-342, 2002, see abstract)." At the time of filing of the instant application there were no general guidelines for successful *in vivo* delivery of antisense compounds known in the art. Problems related to the pharmaceutical use of nucleic acids in general, and antisense and siRNA nucleic acids in particular, are evident from the pre- and post-filing art. One problem is the inability to routinely deliver an effective concentration of a specific nucleic acid into a target cell, such that a target gene or miRNA is inhibited to a degree necessary to produce a therapeutic effect--in this case inhibition of RNA silencing of a gene.

Opalinska et al (Nature Reviews 1:503-514, 2002) teach that: "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA". "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded." (page 511, columns 1-2)

Lu et al (RNA Interference Technology, Cambridge, Appasani, ed., 2005, page 303) state that "Unlike *in vitro* transfection of siRNA into cells, *in vivo* delivery of siRNA into targeted tissue in animal models is much more complicated, involving physical, chemical and biological approaches, and in some cases their combination." Therapeutic applications, however, clearly depend upon optimized local and systemic delivery of siRNA *in vivo*. "...limited reports of *in vivo* studies have indicated a lack of effective delivery methods for siRNA agents." "...the two most critical hurdles are maintaining its [siRNA] stability *in vivo* and delivery to disease tissues and cells." (page 314) Lu et al. admit that while hydrodynamic delivery of siRNA duplexes into mouse liver has proven to be quite efficient, this technique is not clinically feasible in human studies.

Sioud (RNA Silencing, Methods and Protocols, Humana Press, 2005) expresses similar reservations, specifically with respect to the use of cationic carriers, as currently claimed in claims 34 and 35. On page 238, Sioud states "Despite some encouraging results, however, liposomes still have not the characteristics to be perfect carriers because of toxicity, short circulation time, and limited intracellular delivery for target cells." And on page 243, "The *in*

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vivo uptake of siRNAs can differ dramatically with cell types as well as with the status of cell differentiation."

Similarly, Simeoni et al (RNA Silencing, Methods and Protocols, Humana Press, 2005, page 251) state "So far, although siRNA transfection can be achieved with classical laboratory-cultured cell lines using lipid-based formulations, siRNA delivery remains a major challenge for many cell lines and there is still no reasonably efficient method for *in vivo* application."

Gene Therapy

Applicant contemplates that the recombinant nucleic acid composition may be encoded by a vector, and thus Applicant's invention falls within the realm of gene therapy, which is in the nature of transforming cells with nucleic acids encoding therapeutic molecules to produce a therapeutic effect. The claims are drawn to a method for inducing RNA-associated gene silencing effects, wherein the dsRNA will effect post-transcriptional gene silencing of a target gene in a cell or tissue *in vitro* or *in vivo*.

With regard to gene therapy, at the effective filing date of the present application, May 18, 2002, the attainment of any therapeutic effect via gene therapy was, and remains, highly unpredictable, let alone for the attainment of prophylactic effects via gene therapy mechanisms as contemplated by Applicants. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be a difficulty as supported by numerous teachings available in the art. There are several known factors that limit an effective human gene therapy, including sub-optimal vectors, the lack of a stable *in vivo* transgene expression, the adverse host immunological responses to the delivered vectors and most importantly an efficient gene delivery to target tissues or cells. For example, Deonarain (Deonarain, M., Expert Opin. Ther. Pat. 8:53-69, 1998) indicates that:

"[O]ne of the biggest problems hampering successful gene therapy is the ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph).

Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (page 65, CONCLUSION). Verma and Somia (Nature 389: 239-242, 1997) review vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Verma states that:

"the Achilles heel of gene therapy is gene delivery and this is the aspect we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression . . ."

The use of viruses (viral vectors) is a powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells. However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by

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these host responses (e.g., p. 239, col. 3). Even in 2005, Verma and Weitzman (Annu. Rev. Biochem. 74:711-738, 2005) still state:

“The young field of gene therapy promises major medical progress toward the cure of a broad spectrum of human diseases, ranging from immunological disorders to head disease and cancer. It has, therefore, generated great hopes and great hypes, but it has yet to deliver its promised potential”, and “[I]f scientists from many different disciplines participate and pull together as a team to tackle the obstacles, gene therapy will be added to our medicinal armada and the ever- expanding arsenal of new therapeutic modalities.” (page 732, top of third paragraph).

Goncalves (BioEssays 27:506-517, 2005) also states:

"Overall, one can conclude that further improvements in gene transfer technologies (e.g. control over transgene expression and integration) and deeper insights in host-vector interactions (e.g. knowledge on vector and gene-modified cell biodistribution following different routes of administration and the impact on innate and adaptive immunity) are warranted before clinical gene therapy reaches maturity" (page 514, right-hand column, last paragraph).

Gardlik et al (Med. Sci. Monit. 11:RA110-121, 2005) conclude:

"Although clinical trials have already started, there are still numerous limitations that must be solved before routine clinical use. Nevertheless, it can be expected that future research will bring tissue- and disease-specific delivery strategies and that this hurdle will be overcome at last" (page RA119, right-hand column, last paragraph).

Such problems with delivery continue to plague the field of gene therapy. Shoji et al. has characterized the current state of the art as the "tragic failure of gene therapy" because of poor delivery of gene based medicines due to the lack of an appropriate vector that "fulfills the necessary requirements, including high transfection efficiency, non toxicity, non-pathogenicity, non-immunogenicity, [and] non-tumorigenicity." (Shoji et al, Current Pharmaceutical Design 10(7): 785-796, 2004).

Summary

The efficacy of antisense-based therapies hinges upon the ability to deliver a sufficient amount of oligonucleotide to the appropriate tissues and for a sufficient period of time to produce the desired therapeutic effect. Even though the level of skill in the art was high, being that of a Ph.D. or M.D., the artisan would find the art to be generally of a low level of predictability for the use of dsRNAs, alone or encoded in expression vectors, for the treatment of any disorder. So far, it appears that all of the developments in nucleic acid-based therapies have not been sufficient to overcome this one basic obstacle—drug delivery. The art teaches that the behavior of oligonucleotide-based compositions and their delivery *in vivo* are unpredictable, therefore claims to pharmaceutical compositions and methods of treating diseases by the administration of oligonucleotide-based pharmaceuticals are subject to the question of enablement due to the high level of unpredictability associated with this technique as taught in the prior art.

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In view of the express teachings of the post-filing art suggesting that *in vivo* delivery of dsRNA, by itself or encoded in an expression vector, is unpredictable, it is essential that the instant application provide enabling disclosure showing how to use the pharmaceutical compositions of the instant invention to target any desired gene in any cell in any animal to effect the desired outcome. The skilled artisan would not know *a priori* whether introduction of oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the oligonucleotide crossing the enormous genus of anatomically and physiologically distinct blood-brain and/or blood-retina barriers to reach the desired retinal cell in the enormous genus of anatomically distinct animals in a sufficient concentration and remaining for a sufficient time to activate target-specific RNA interference of any desired gene. Specific guidance would be required to teach one of skill in the art how to deliver double-stranded RNA molecules to cells *in vivo* to produce a measurable effect in an organism. The state of the art is such that successful delivery of dsRNA *in vivo* or *in vitro* such that the oligonucleotide provides the requisite biological effect to the target cells/tissues/organs must be determined empirically.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

The quantity of experimentation required to practice the invention as claimed, based upon what is known in the art and what has been disclosed in the specification, will create an undue burden for a person of ordinary skill in the art because it would require the artisan to experiment to identify the target gene responsible for any one of an enormous genus of etiologically and pathologically distinct retinal diseases, determine the structures of the mRNA targets that are associated with a particular condition or disease for which therapy is sought, determine the dsRNA nucleic acid sequence(s) that would specifically actuate post-transcriptional gene silencing of the target gene, determine those vectors and expression control elements that could be used to efficiently express the dsRNA in the desired retinal cell type, and identify modes of delivery *in vivo* such that the expression of desired target gene is inhibited at a significant level and for a sufficient amount of time to produce the desired therapeutic effect so as to treat the enormous genus of retinal diseases in the enormous genus of animals. Neither the specification as filed, nor the prior art searched, provides any specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Response to Arguments

Applicant argues that such a method for delivery of oligoribonucleotides across the blood-brain or the blood-retina barrier can be used for any intended target gene or purpose, and it is moot as to what the target sequence is.

Applicant's argument(s) has been fully considered, but is not persuasive. Dependent claims 5-6 and 50-53 require that the dsRNA inhibit the expression of a target gene in a

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sufficient amount to treat one or more degenerative retinal diseases. As discussed in the rejection, the art teaches that the behavior of oligonucleotide-based compositions and their delivery *in vivo* are unpredictable, therefore claims to pharmaceutical compositions and methods of treating diseases by the administration of oligonucleotide-based pharmaceuticals are subject to the question of enablement due to the high level of unpredictability associated with this technique as taught in the prior art.

The specification is not considered to be enabling for treating an enormous genus of eye disorders in the enormous genus of animals possessing eyes. Given the complexity of the biochemistry of such disorders, the distinctly different anatomical properties that comprise blood-retina barriers in the enormous genus of animal subjects, and the many genes expressed in the eye which may or may not be directly related to the disorders, one of skill would require specific guidance as to how to design the dsRNAs effective for inhibiting the expression of a specific gene involved in a specific disorder in order to treat the specific disorder. Such comprehensive disclosure is lacking.

The specification is not enabling because it does not disclose those formulations and nucleic acid molecule concentrations necessary to overcome the art-recognized unwanted side effects outside the target organs eye and brain-often without significant quantities of active substance being detectable in the target tissue. The disclosed target gene, eGFP, is an exogenous gene, and thus does not reflect the existence of unwanted side effects caused by the expression of a developmentally important gene in the clinically relevant, real world.

The efficacy of antisense-based therapies hinges upon the ability to deliver a sufficient amount of oligonucleotide to the appropriate tissues and for a sufficient period of time to produce the desired therapeutic effect. In view of the express teachings of the post-filing art suggesting that *in vivo* delivery of dsRNA, by itself or encoded in an expression vector, is unpredictable, it is essential that the instant application provide enabling disclosure showing how to use the pharmaceutical compositions of the instant invention to target any desired gene in any cell in any animal to effect the desired outcome. The skilled artisan would not know *a priori* whether introduction of oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the oligonucleotide crossing the enormous genus of anatomically and physiologically distinct blood-brain and/or blood-retina barriers to reach the

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desired retinal cell in the enormous genus of anatomically distinct animals in a sufficient concentration and remaining for a sufficient time to activate target-specific RNA interference of a specific desired gene. Specific guidance would be required to teach one of skill in the art how to deliver double-stranded RNA molecules to cells *in vivo* to produce a measurable effect in an organism. The state of the art is such that successful delivery of dsRNA *in vivo* or *in vitro* such that the oligonucleotide provides the requisite biological effect to the target cells/tissues/organs must be determined empirically. In the absence of the necessary specific guidance, and in light of the art-recognized unpredictability in the field, the artisan would have to perform undue experimentation to use the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the Applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the Applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. **Claims 2, 7, 13, 21-22, 24-28, 31 and 54 stand rejected under 35 U.S.C. 102(b)** as being anticipated by Carter (U.S. Patent No. 5,712,257).

This rejection is maintained for reasons of record in the office action mailed January 24, 2008 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed July 24, 3008.

With respect to claim 2, Carter discloses a method for delivery of oligoribonucleotides across the blood-brain or the blood-retina barrier, wherein a composition comprising one or more double-stranded oligoribonucleotides (dsRNA) is introduce into a cell, tissue or organism outside the blood-brain or blood-retina barrier.

With respect to claim 7, 24 and 26, Carter discloses that the art has practiced administering dsRNA by injection into a patient's bloodstream (col. 1, lines 37-38) and that the composition may also be topically administered (col. 7, line 1), in a form to be applied outside the eyeball, e.g. eye drops (col. 7, line 34). Thus, the carrier and/or dsRNA-binding molecules

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were selected such that the dsRNA molecules are delivered continuously to the target cells or tissues over a defined period of time.

With respect to claim 13, Carter discloses the dsRNA may be between 21-23 nucleotides in length (col. 7, line 51-col. 8, line 14).

With respect to claims 21-22, Carter discloses the dsRNA is complexed with a surfactant forming a micelle (col. 1, lines 55-56), wherein the surfactant may be anionic, cationic or non-ionic (col. 1, lines 63-64; col. 3, lines 20-42).

With respect to claim 25, Carter discloses the ternary complex may further comprise a component that provides specific tropism or attraction for a certain cell class (col. 4, lines 55-63).

With respect to claims 27-28 and 31, Carter discloses the cells, tissue or organism may be mammalian, e.g. mouse or human (col. 3, line 18; col. 6, line 33; col. 7, line 17; col. 8, line 43), wherein one of ordinary skill in the art recognizes mammals to be vertebrates.

With respect to claim 54, Carter discloses the dsRNA may be complexed with liposomes (col. 13, lines 49-50).

Response to Arguments

Applicant argues that Carter fails to teach how to deliver dsRNA across the blood-brain or the blood-retina barrier. Moreover, there is no indication that dsRNA can even cross the blood-brain or the blood-retina barrier.

Applicant's argument(s) has been fully considered, but is not persuasive. The instant specification fails to disclose an essential feature to confer trafficking of dsRNA across the blood-brain or blood-retina barrier, and thus such trafficking is considered an inherent and natural feature of the biological system, that is to say, normal physiology and cell biology. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of the invention, but only that the subject matter is in fact inherent in the prior art reference. This inherency argument is bolstered by *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003). Inherent anticipation does not require recognition in the prior art. Furthermore, see *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970, 58 USPQ2d 1865 (Fed. Cir. 2001), "a limitation or the entire invention is inherent and in the public domain if it is the "natural result flowing from" the explicit disclosure of the prior art". Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). In the instant case, Carter et al discloses means of administering dsRNA by the same means to the same cells or tissues of the eye, and thus has disclosed the active method steps recited in the claims. Thus, absent evidence to the

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contrary, the dsRNA of Carter et al administered by injection into a patient's bloodstream or topically, e.g. eye drops, would inherently and necessarily traffick across the blood-brain or blood-retina barriers.

9. Claims 2-3, 5-10, 13, 19-22, 24, 26-28, 31 and 50-54 stand rejected under 35 U.S.C. 102(a) and 35.U.S.C 102(e) as being anticipated by LaFleur et al (U.S. Patent No. 6,433,145 B1)

This rejection is maintained for reasons of record in the office action mailed January 24, 2008 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed July 24, 3008.

With respect to claim 2, LaFleur et al discloses a method for delivery of oligoribonucleotides across the blood-brain or the blood-retina barrier, wherein a composition comprising one or more double-stranded oligoribonucleotides (dsRNA) is introduce into a cell, tissue or organism outside the blood-brain or blood-retina barrier (col. 9, line 52; col. 102, line 14).

With respect to claim 3, LaFleur et al disclose the method results in the provision of a test cell, tissue or organism, which can be preferably maintained under conditions allowing the degradation of the corresponding mRNA of one or more of target genes by RNA interference. An embodiment of the invention is an isolated cell or tissue of a subject or animal model wherein the agent may be administered over a long-term period (col. 77, lines 29-30). Furthermore, the cells may be used to screen for KDI antagonists (col. 138, line 25).

With respect to claims 5-6, LaFleur et al disclose the dsRNA specifically modulates or inhibits target gene expression, wherein the target cellular mRNA may encode KDI (col. 140, lined 23).

With respect to claims 7-9, LaFleur et al disclose the cells and/or tissues are from the retina (col. 118, lines 35-37; col. 130, lines 37-46),

With respect to claim 10, LaFleur et al do not use the terms "retinal pigment epithelium" nor "neurosensory retina cells"; however, one of ordinary skill in the art readily understands that the retina tissue comprises "retinal pigment epithelium" and "neurosensory retina cells". Thus, the disclosure of LaFleur et al reasonably embraces such limitations, absent evidence to the contrary.

With respect to claim 13, LaFleur et al disclose the dsRNA molecules are at least 15 nucleotides, more preferably at least about 20 nucleotides (col. 15, lines 3-4; col. 17 lines 19-20). The antisense approach is used to inhibit translation of endogenous target gene mRNA, e.g. KDI, wherein the oligonucleotides range from about 6 to about 50 nucleotides in length (col. 141, lines 5-8, 15-17).

With respect to claims 19-20, LaFleur et al disclose the inventive nucleic acids may be inserted into vectors and operably linked to a tissue-specific promoter (col.s 75-76; col 101, lines 57-67; col. 140, lines 23-25).

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With respect to claims 21-22 and 54, LaFleur et al disclose the dsRNA may be combined with one or more suitable carriers, wherein the carrier may be a liposome (col. 76, lines 25-32).

With respect to claim 24, LaFleur et al disclose that various delivery systems are known and can be used to administer a compound of the invention, e.g. encapsulation in liposome particles, intravenous or subcutaneous routes, e.g. topical drops and eyedrop form, wherein the composition may be provided by continuous subcutaneous infusion, or continuous infusion into the aqueous humor in order to increase the local concentration of the polynucleotide in the retina, wherein the carrier may be specific for the retinal cells, e.g. by targeting a specific receptor (col. 76, lines 25-40; col. 77, line 55; col. 79, lines 32-33).

With respect to claim 26, LaFleur et al disclose the agent may be administered by different routes, e.g. systemically injection or topically, e.g. as eyedrops (col. 107, line 19; col. 119, line 38).

With respect to claims 27-28 and 31, LaFleur et al disclose the subject may be human (col. 78, line 48).

With respect to claims 50-53, LaFleur et al disclose the polynucleotides of the invention may be used in the treatment of retinal diseases such as macular degeneration and retinoblastoma (col. 118, lines 35-37).

Response to Arguments

Applicant argues that LaFleur et al fails to teach how to deliver dsRNA across the blood-brain or the blood-retina barrier. Moreover, there is no indication that dsRNA can even cross the blood-brain or the blood-retina barrier.

Applicant's argument(s) has been fully considered, but is not persuasive. The instant specification fails to disclose an essential feature to confer trafficking of dsRNA across the blood-brain or blood-retina barrier, and thus such trafficking is considered an inherent and natural feature of the biological system, that is to say, normal physiology and cell biology. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of the invention, but only that the subject matter is in fact inherent in the prior art reference. This inherency argument is bolstered by *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003). Inherent anticipation does not require recognition in the prior art. Furthermore, see *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970, 58 USPQ2d 1865 (Fed. Cir. 2001), "a limitation or the entire invention is inherent and in the public domain if it is the "natural result flowing from" the explicit disclosure of the prior art". Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). In the instant case, LaFleur et al discloses

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means of administering dsRNA by the same means to the same cells or tissues of the eye, and thus has disclosed the active method steps recited in the claims. Thus, absent evidence to the contrary, the dsRNA of LaFleur et al administered by injection into a patient's bloodstream or topically, e.g. eye drops, would inherently and necessarily traffick across the blood-brain or blood-retina barriers.

10. Claims 2-13, 21-22, 24, 26-28, 31, 46, 50 and 54 stand rejected under 35 U.S.C. 102(a) and 35.U.S.C 102(e) as being anticipated by King (U.S. 2002/0165158 A1).

This rejection is maintained for reasons of record in the office action mailed January 24, 2008 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed July 24, 3008.

With respect to claim 2, King discloses a method for delivery of oligoribonucleotides across the blood-brain or the blood-retina barrier, wherein a composition comprising one or more double-stranded oligoribonucleotides (dsRNA) is introduce into a cell, tissue or organism outside the blood-brain or blood-retina barrier, wherein the preferred embodiment is retinal tissue (pg 1, [0009]).

With respect to claim 3, King discloses the method results in the provision of a test cell, tissue or organism, which can be preferably maintained under conditions allowing the degradation of the corresponding mRNA of one or more of target genes by RNA interference. An embodiment of the invention is an isolated cell or tissue of a subject or animal model (pg 4, [0039], [0060]; pg 5, [0081-82]), wherein the agent may be administered over a long-term period (pg 4, [0049]).

With respect to claims 4 and 46, King discloses the method provides for the identification or validation of the function of a gene and drug discovery, the method further comprising comparing the resulting phenotype produced in the test cell, tissue or organism with that of a suitable control, thus allowing information on the function of the gene to be gained. The method may be used to evaluate an agent, e.g. screening for an agent, the method comprising determining if the agent modulates the expression of a target gene (pg 5, [0075], [0082]). Abnormal expression levels in the subject are compared to a control (pg 5, [0066], [0084]).

With respect to claims 5-6, King discloses the dsRNA specifically modulates or inhibits target gene expression, wherein the target cellular mRNA may encode Protein Kinase C (PKC) isoforms or Retinoblastoma (Rb) (pg 1, [0006]; pg 3, [0026]).

With respect to claims 7-9, King discloses the agent is targeted to retinal tissue (pg 3, [0033]),

With respect to claim 10, King does not recite the terms "retinal pigment epithelium" nor "neurosensory retina cells"; however, one of ordinary skill in the art readily understands that the retina tissue comprises "retinal pigment epithelium" and "neurosensory retina cells". Thus, the disclosure of King reasonably embraces such limitations, absent evidence to the contrary.

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With respect to claims 11-12, King does not disclose that PKC β and/or Rb are predominantly expressed in retinal cells or tissues. However, at the time of the invention, one of ordinary skill in the art recognized that PKC β and Rb are highly expressed in retinal cells.

With respect to claim 13, King discloses the dsRNA molecules are between about 20 to 25 nucleotides (pg 9, [0123]), specifically 21-23 nucleotides (pg 10, [0129]).

With respect to claim 19, King discloses the inventive nucleic acids may be inserted into vectors, wherein the expression of the nucleic acid is operably linked to a promoter (pg 2, [0017]; pg 3, [0025]; pg 17, [0192]).

With respect to claims 21-22 and 54, King discloses the dsRNA may be combined with one or more suitable carriers, wherein the carrier may be a liposome (pg 10, [0126]; pg 16, [0183-0194]; pg 18, [0202]), and wherein the carrier may be specific for the retinal cells, e.g. as eyedrops and/or liposomes tagged with antibodies against cell surface antigens of the target tissue (pg 10, [0124-0127]; pg 18, [0202]).

With respect to claim 24, King discloses the carrier may comprise compounds that achieve controlled release (pg 17, [0191]), wherein the period over which the agent is administered can be long term (pg 3, [0036]).

With respect to claim 26, King discloses the agent may be administered by different routes, e.g. intravenous or administered to the eye as eyedrops (pg 10, [0124-0127]).

With respect to claims 27-28 and 31, King discloses the subject may be human (pg 2, [0021]).

With respect to claim 50, King discloses the inhibition of the target gene expression is associated with retinal disease, e.g. ischemic retinopathy and retinopathy-of-prematurity, (pg 1, [0010], pg 4, [0059]).

Response to Arguments

Applicant argues that King fails to teach how to deliver dsRNA across the blood-brain or the blood-retina barrier. Moreover, there is no indication that dsRNA can even cross the blood-brain or the blood-retina barrier.

Applicant's argument(s) has been fully considered, but is not persuasive. The instant specification fails to disclose an essential feature to confer trafficking of dsRNA across the blood-brain or blood-retina barrier, and thus such trafficking is considered an inherent and natural feature of the biological system, that is to say, normal physiology and cell biology. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of the invention, but only that the subject matter is in fact inherent in the prior art reference. This inherency argument is bolstered by *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003). Inherent anticipation does not require recognition in the prior art. Furthermore, see *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970, 58 USPQ2d 1865 (Fed. Cir. 2001), "a limitation or the entire invention is inherent

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and in the public domain if it is the "natural result flowing from" the explicit disclosure of the prior art". Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). In the instant case, King discloses means of administering dsRNA by the same means to the same cells or tissues of the eye, and thus has disclosed the active method steps recited in the claims. Thus, absent evidence to the contrary, the dsRNA of King administered by injection into a patient's bloodstream or topically, e.g. eye drops, would inherently and necessarily traffick across the blood-brain or blood-retina barriers.

11. Claims 2, 5-10, 13, 19-22, 24, 26-28, 31 and 48-54 stand rejected under 35 U.S.C. 102(e) as being anticipated by Tolentino et al (U.S. Patent No. 7,148,342 B2).

This rejection is maintained for reasons of record in the office action mailed January 24, 2008 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed July 24, 3008.

With respect to claim 2, Tolentino et al discloses a method for delivery of oligoribonucleotides across the blood-brain or the blood-retina barrier, wherein a composition comprising one or more double-stranded oligoribonucleotides (dsRNA) is introduce into a cell, tissue or organism outside the blood-brain or blood-retina barrier, wherein the preferred embodiment is retinal tissue (pg 1, [0009]).

With respect to claims 5-6, King discloses the dsRNA specifically modulates or inhibits target gene expression, wherein the target cellular mRNA may encode VEGF, Flt-1 and Flk/KDR genes (col. 2, lines 45-47).

With respect to claims 7-9 and 50-53, Tolentino et al disclose the compositions of the invention are used for the treatment of retinal diseases such as age-related macular degeneration (col. 2, lines 47-50).

With respect to claim 10, Tolentino et al do not use the terms "retinal pigment epithelium" nor "neurosensory retina cells"; however, one of ordinary skill in the art readily understands that the retina tissue comprises "retinal pigment epithelium" and "neurosensory retina cells". Thus, the disclosure of Tolentino et al reasonably embraces such limitations, absent evidence to the contrary.

With respect to claim 13, Tolentino et al disclose the dsRNA molecules are less than 30 nucleotides, about 19 to about 25 nucleotides, e.g. 21-22 nucleotides (col. 2, lines 8, 25 and 57-58; col. 7, line 15).

With respect to claims 19-20, King discloses the inventive nucleic acids may be inserted into vectors, wherein the expression of the nucleic acid is operably linked to a promoter, e.g. a tissue-specific promoter (col. 9, lines 37-47).

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With respect to claims 21-22 and 54, Tolentino et al disclose the dsRNA may be combined with one or more suitable carriers, wherein the carrier may be a liposome (col. 13, lines 37-50), and wherein the carrier may comprise a ligand molecule that can target the carrier to a particular cell or tissue (col. 13, lines 56-58).

With respect to claim 24, King discloses the carrier may comprise compounds that achieve controlled release, wherein the period over which the agent is administered can be long term, e.g. osmotic pumps, pellets or suppositories (col. 15, lines 28-35).

With respect to claim 26, Tolentino et al disclose the agent may be administered by different routes, e.g. regional or systemic, intravenous (col. 12, line 39; col. 15, lines 15-35).

With respect to claims 27-28 and 31, Tolentino et al disclose the subject may be human (col. 11, line 60).

With respect to claim 48, Tolentino et al disclose the dsRNA comprises two symmetrical 3' overhangs of two nucleotides in length (col. 5, lines 45-60).

With respect to claim 49, Tolentino et al disclose the 3' overhangs may be 2'-deoxythymidine (col. 6, line 3).

Response to Arguments

Applicant argues that Tolentino et al fails to teach how to deliver dsRNA across the blood-brain or the blood-retina barrier. Moreover, there is no indication that dsRNA can even cross the blood-brain or the blood-retina barrier.

Applicant's argument(s) has been fully considered, but is not persuasive. The instant specification fails to disclose an essential feature to confer trafficking of dsRNA across the blood-brain or blood-retina barrier, and thus such trafficking is considered an inherent and natural feature of the biological system, that is to say, normal physiology and cell biology. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of the invention, but only that the subject matter is in fact inherent in the prior art reference. This inherency argument is bolstered by *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003). Inherent anticipation does not require recognition in the prior art. Furthermore, see *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970, 58 USPQ2d 1865 (Fed. Cir. 2001), "a limitation or the entire invention is inherent and in the public domain if it is the "natural result flowing from" the explicit disclosure of the prior art". Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). In the instant case, Tolentino et al discloses means of administering dsRNA by the same means to the same cells or tissues of the eye, and thus has disclosed the active method steps recited in the claims. Thus, absent evidence to the

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contrary, the dsRNA of Tolentino et al administered by injection into a patient's bloodstream or topically, e.g. eye drops, would inherently and necessarily traffick across the blood-brain or blood-retina barriers.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. **Claims 2-13, 19-22, 24, 26-28, 31, 46 and 48-54 stand rejected under 35 U.S.C. 103(a)** as being unpatentable over Robinson et al (U.S. Patent No. 5,814,620) in view of LaFleur et al (U.S. 6,433,145 B1) and Tuschl et al (U.S. 2002/0086356 A1).

This rejection is maintained for reasons of record in the office action mailed January 24, 2008 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed July 24, 2008.

Determining the scope and contents of the prior art.

Robinson et al disclose a method for delivery of oligoribonucleotides across the blood-brain or the blood-retina barrier into cells and/or tissues of the eye, wherein a composition comprising one or more antisense oligoribonucleotides are introduced into a cell, tissue or organism outside the blood-brain or blood-retina barrier, wherein the preferred embodiment is retinal tissue. The method of the invention is used for the treatment of retinal diseases such as

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age-related macular degeneration (col. 2, lines 36-37; col. 11, lines 15-20). Robinson et al disclose the method yields a test organism maintained under conditions allowing the degradation of the corresponding target gene mRNA (col. 11, line 30-col. 12, lined 15). The antisense nucleic acids are from about 15 to about 25 nucleotides in length, and may be chemically modified (col. 3, line 45-col. 4, line 14). The antisense nucleic acids are targeted against a cellular gene such as VEGF, thereby inhibiting expression of VEGF in the retina (col. 4, lines 23-26), and may be administered to the patient, e.g. human, locally or systemically (col. 3, lines 35-37; col. 4, lines 35-42), wherein the formulation may comprise a carrier, e.g. a liposome (col. 9, line 13) and/or slow-release polymers (col. 11, line 13).

Robinson et al do not disclose:

- i) the antisense nucleic acid is double-stranded RNA,
- ii) the dsRNA nucleic acid is encoded by a vector,
- iii) the dsRNA is operably linked to a tissue-specific promoter,
- iv) the carrier is specific for the cells and/or tissues, and
- v) the method is used in drug discovery or target gene validation.

However, at the time of the invention, LaFleur et al disclosed a method for the specific modulation of the expression of target genes in cells and/or tissues of the eye, wherein a composition comprising one or more double-stranded oligoribonucleotides (dsRNA) is introduced into a cell, tissue or organism outside the blood-brain or blood-retina barrier (col. 9, line 52; col. 102, line 14), wherein the method results in the provision of a test cell, tissue or organism, which can be preferably maintained under conditions allowing the degradation of the corresponding mRNA of one or more of target genes by RNA interference. An embodiment of the invention is an isolated cell or tissue of a subject or animal model wherein the agent may be administered over a long-term period (col. 77, lines 29-30). Furthermore, the cells may be used to screen for KDI antagonists (col. 138, line 25).

LaFleur et al disclose the dsRNA specifically modulates or inhibits target gene expression, wherein the target cellular mRNA may encode KDI (col. 140, lined 23), wherein the dsRNA molecules are at least 15 nucleotides, more preferably at least about 20 nucleotides (col. 15, lines 3-4; col. 17 lines 19-20). The antisense approach is used to inhibit translation of endogenous target gene mRNA, e.g. KDI, wherein the oligonucleotides range from about 6 to about 50 nucleotides in length (col. 141, lines 5-8, 15-17), wherein one or more nucleotide bases may be modified (col. 9, lines 60-65; col. 141-142). The inventive nucleic acids may be inserted into vectors and operably linked to a tissue-specific promoter (col.s 75-76; col 101, lines 57-67; col. 140, lines 23-25) and/or may be combined with one or more suitable carriers, wherein the carrier may be a liposome (col. 76, lines 25-32). Various delivery systems are known and can be used to administer a compound of the invention, e.g. encapsulation in liposome particles, systemically by intravenous or subcutaneous routes, e.g. topical drops and eye drop form, wherein the composition may be provided by continuous subcutaneous infusion, or continuous infusion into the aqueous humor in order to increase the local concentration of the polynucleotide in the retina, wherein the carrier may be specific for the retinal cells, e.g. by targeting a specific receptor (col. 76, lines 25-40; col. 77, line 55; col. 79, lines 32-33; col. 107, line 19; col. 119, line 38). The polynucleotides of the invention may be used in the treatment of cells and/or tissues

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from the retina (col. 118, lines 35-37; col. 130, lines 37-46), e.g. retinal diseases such as macular degeneration and retinoblastoma (col. 118, lines 35-37).

Neither Robinson et al nor LaFleur et al disclose:

- i) the method may be used for the identification or validation of the function of a gene,
- ii) the target gene is expressed predominantly or specifically in the eye,
- iii) the dsRNA contains two symmetrical 3' overhangs, and
- iv) the dsRNA 3' overhangs are 2'-deoxythymidine.

However, at the time of the invention, Tuschl et al disclosed methods of using single-stranded and double-stranded RNA molecules to mediate gene-silencing of a target gene expression to examine the function of a gene, to assess whether an agent acts on a gene and to validate targets for drug discovery (pg 2, [0010]), wherein the phenotype of the test cell or organism is then observed and compared to that of an appropriate control cell or organism (pg 2, [0010-0011]). The single-stranded and double-stranded RNA molecules are about 21 to about 23 nucleotides, wherein both strands of the dsRNA have a 3' overhang of two nucleotides, wherein the 3' overhang nucleotides may be substituted for 2'-deoxythymidine (pg 5, [0055]). Tuschl et al disclose that any cellular gene, e.g. an oncogene or the mRNA of any protein associated with or causative of a disease or undesirable condition, can be targeted for degradation using gene-silencing RNAs (pg 6, [0061]).

Ascertaining the differences between the prior art and the claims at issue.

LaFleur et al do not use the terms "retinal pigment epithelium" nor "neurosensory retina cells"; however, one of ordinary skill in the art readily understands that the retina tissue anatomically comprises "retinal pigment epithelium" and "neurosensory retina cells". Thus, the disclosure of LaFleur et al reasonably embraces such limitations, absent evidence to the contrary.

Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals, possessing advanced degrees, including M.D.'s and Ph.D.'s. They will be medical doctors, scientists, or engineers. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in designing, formulating and administering gene-silencing RNA nucleic acids to mammalian subjects, as well as anatomical and physiological knowledge of the circulatory and ocular organ systems. Therefore, the level of ordinary skill in this art is high.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute an antisense gene-silencing RNA as taught by Robinson et al with a double-stranded gene-silencing RNA as taught by LaFleur et al with a reasonable chance of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. One of ordinary skill in the art recognized that, in general, siRNAs and antisense oligonucleotides can be used to produce the same effect, albeit with different potencies and by different biochemical mechanisms. siRNAs and antisense

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oligonucleotides can both be used to inhibit gene expression *in vivo* or *in vitro*, via mRNA degradation or translation attenuation, and, thus, both types of nucleic acids may be used to prevent the expression of a gene in a cell (Tuschl et al). Thus, in this sense, siRNAs and antisense oligonucleotides are art-recognized equivalents that may be used for the same purpose: reducing or inhibiting gene expression. (See for example MPEP §2144.06, SUBSTITUTING EQUIVALENTS KNOWN FOR THE SAME PURPOSE.) An artisan would be motivated to substitute gene-silencing antisense RNAs for gene-silencing dsRNA or a vector expressing a gene-silencing dsRNA because dsRNAs are extraordinarily powerful reagents for mediating gene silencing and are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments (see for example, Tuschl et al, Figures 8A and 8B).

It also would have been obvious to try administering a gene-silencing dsRNA targeted against a disease-causing gene that is predominantly or specifically expressed in the eye because “a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipate success, it is likely that product not of innovation but of ordinary skill and common sense.” At the time of the invention, those of ordinary skill in the art were well aware that gene-silencing dsRNAs may be designed to target a disease-causing mRNA for degradation. An artisan would be motivated to try administering a gene-silencing dsRNA targeted against a disease-causing gene that is predominantly or specifically expressed in the eye because the patient would be less likely to suffer from adverse, non-specific side effects due to off-target responses in non-retinal cells while simultaneously achieving degradation of the intended target gene, thereby treating the disease or disorder that the patient is suffering from.

It also would have been obvious to combine the method of inhibiting the expression of a target gene in a retinal cell to further provide for a test cell, tissue or organism from which to identify or validate the function of a gene with a reasonable chance of success because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Furthermore, LaFleur et al and Tuschl et al disclose that methods of using gene-silencing RNAs may be used is gene and drug discovery and validation assay methods. An artisan would be motivated to use gene-silencing dsRNAs in gene and drug discovery and validation assay methods because it is technically easier and less costly to temporarily silence a novel gene with a specific dsRNA than it is to generate a genetically-modified genomic loss-of-function cell, tissue or organism for each and every gene the artisan wishes to assay in the screening methods.

Thus, the invention as a whole is *prima facie* obvious.

Response to Arguments

Applicant argues that Robinson et al and LaFleur et al fail to teach how to deliver dsRNA across the blood-brain or the blood-retina barrier. Moreover, there is no indication that dsRNA can even cross the blood-brain or the blood-retina barrier.

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Applicant's argument(s) has been fully considered, but is not persuasive. The instant specification fails to disclose an essential feature to confer trafficking of dsRNA across the blood-brain or blood-retina barrier, and thus such trafficking is considered an inherent and natural feature of the biological system, that is to say, normal physiology and cell biology. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of the invention, but only that the subject matter is in fact inherent in the prior art reference. This inherency argument is bolstered by *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003). Inherent anticipation does not require recognition in the prior art. Furthermore, see *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970, 58 USPQ2d 1865 (Fed. Cir. 2001), "a limitation or the entire invention is inherent and in the public domain if it is the "natural result flowing from" the explicit disclosure of the prior art". Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). In the instant case, Robinson et al and LaFleur et al disclose means of administering gene silencing RNA by the same means to the same cells or tissues of the eye, and thus have disclosed the active method steps recited in the claims. Thus, absent evidence to the contrary, the dsRNA of LaFleur et al administered by injection into a patient's bloodstream or topically, e.g. eye drops, would inherently and necessarily traffick across the blood-brain or blood-retina barriers.

Applicant does not contest the teachings of Tuschl et al as applied to methods of using single-stranded and double-stranded RNA molecules to mediate gene-silencing of a target gene expression to examine the function of a gene, to assess whether an agent acts on a gene and to validate targets for drug discovery (pg 2, [0010]), wherein the phenotype of the test cell or organism is then observed and compared to that of an appropriate control cell or organism (pg 2, [0010-0011]). The single-stranded and double-stranded RNA molecules are about 21 to about 23 nucleotides, wherein both strands of the dsRNA have a 3' overhang of two nucleotides, wherein the 3' overhang nucleotides may be substituted for 2'-deoxythymidine (pg 5, [0055]). Tuschl et al disclose that any cellular gene, e.g. an oncogene or the mRNA of any protein associated with or causative of a disease or undesirable condition, can be targeted for degradation using gene-silencing RNAs (pg 6, [0061]).

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Double Patenting

13. **The prior provisional rejection of Claims 2, 5-13, 21-22, 25-28, 31, 48 and 50-53 on the ground of nonstatutory obviousness-type double patenting** as being unpatentable over claims 1, 5-6, 9, 16 and 96 of copending Application No. 10/511,657 (U.S. 2006/0003915 A1) **is withdrawn** in light of Applicant's filing of a Terminal Disclaimer.

Terminal Disclaimer

The terminal disclaimer filed on July 24, 2008 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of copending Application No. 10/511,657 (U.S. 2006/0003915 A1) has been reviewed and is accepted. The terminal disclaimer has been recorded.

Conclusion

14. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill, Ph.D./

Examiner, Art Unit 1633

/Q. JANICE LI, M.D./

Primary Examiner, Art Unit 1633